

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 2 of 17

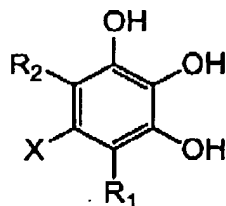
Attorney's Docket No.: 17170-002001

Amendments to the Claims:

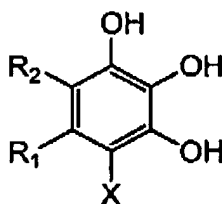
This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

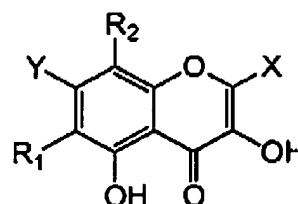
1. (Currently amended) A method of treating amyloidosis associated with Alzheimer's disease and islet amyloid fibrils, in a mammal suffering therefrom, comprising administration to the mammal of a therapeutically effective amount of an isolated pure compound selected from the group consisting of the compounds of formula A, formula B, formula C, formula D, and formula E:



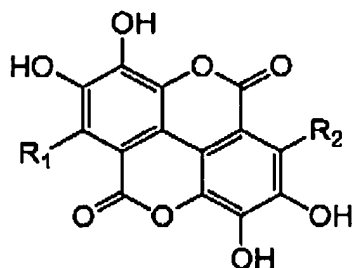
Formula A



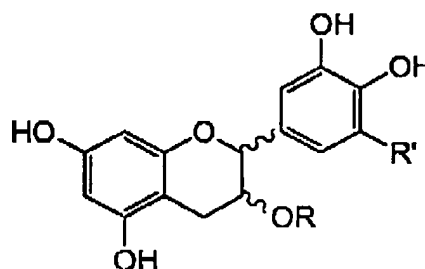
Formula B



Formula C



Formula D



Formula E

where:

R is selected from the group consisting of hydrogen, 2,3-dihydroxybenzoyl, 3,4-dihydroxybenzoyl, 2,3,4-trihydroxybenzoyl, and 3,4,5-trihydroxybenzoyl;

R' is hydrogen or OH;

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 3 of 17

Attorney's Docket No.: 17170-002001

~~R₁ and R₂ are independently selected from hydrogen and non-interfering substituents;~~

X is selected from hydrogen and the group consisting of

- (a) hydroxy, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, and cycloamino,
- (b) C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₁₋₂₂ alkylthio, and C₁₋₂₂ alkylcarboxyl, each optionally substituted with 1 to 5 moieties selected from the group consisting of halogen, hydroxy, mercapto, amino, nitro, C₁₋₆ alkoxy, C₁₋₆ alkylthio, and C₁₋₆ alkylcarboxyl,
- (c) aromatic and heteroaromatic groups substituted with 2 or 3 adjacent hydroxy groups, and optionally substituted with 1 to 5 non-interfering substituents,
- (d) sugars, optionally substituted with one or more anionic groups selected from sulfate, phosphate, phosphonate, carboxylate, and sulfonate groups,
- (e) peptides and peptide derivatives, and
- (f) -C(O)R₃ and -C(O)OR₃, where R₃ is selected from the group consisting of (a) through (e) above; and

Y is hydrogen, hydroxy, C₁₋₆ alkoxy, benzyloxy, where the phenyl group is optionally substituted with 1 to 3 substituents selected from halo and C₁₋₆ alkyl, or -OSO₂R₄, where R₄ is C₁₋₆ alkyl or phenyl optionally substituted with 1 to 3 substituents selected from halo and C₁₋₆ alkyl;

and the group of compounds consisting of acacetin, actinorhodine, alizarin, alizarin blue, alizarin orange, alizarinsulfonic acid, alkannin, anthragallol, anthralin, anthrarobin, antharufin, apigenin, apigetrin, apiose, baicalein, baptigenin, 1,2,4-benzenetriol, bostrycoidin, carbidopa, carminic acid, carubicin, cellobiose, centaurein, chloranilic acid, chondrosine, chromotrope 2B, chromotropic acid, chrysamminic acid, chrysarobin, chrysin, chrysophanic acid, cichoriin, citrazinic acid, citromycetin, collinomycin, curvularin, cyanidin, cyanidin 3-glucoside, cyanidin 3-rhamnoglucoside, cyanidin 3,5-diglucoside, cyanidin 3-sophoroside, daphnetin, datiscetin, daunorubicin, delphinidin, deoxyepinephrine, diosmetin, diosmin, dioxethedrine, dopa, dopamine, doxorubicin, droxidopa, echinochrome A, embelin, emodin, ergoflavin, eriodictyol, esculetin, fenoldopam, fomecin A, fomecin B, fraxetin, fraxin, fredericamycin A, fumigatin, fusarubin, fuscine, fustin, galangin, gallein, gallocyanine, gardenin A, gardenin B, gardenin C, gardenin D, gardenin E, genistein, gentisin, granaticin, guamecyclyne, hematein,

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 4 of 17

Attorney's Docket No.: 17170-002001

hydroxysophorobioside, hydroxysophoricoside, icariin, isoquercitrin, kaempferol, kermesic acid, laccaic acid A, laccaic acid B, laccaic acid C, laccaic acid D, leucocyanidin, luteolin, maclurin, menogaril, methylenedigallic acid, morin, oosporein, phenicin, phloroglucide, puberulic acid, puberulonic acid, purpurin, purpurogallin, quercetagenin, quercimritrin, quinalizarin, quinic acid, resistomycin, rhamnetin, rhein, rhodizonic acid, rhodomycin A, rhodomycin B, robinin, ruberythric acid, rufigallol, rutin, scutellarein, tannic acid, tetroquinone, tiron, troxerutin, and tunichrome B1,

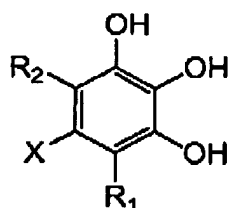
but excluding pyrogallol,

and the pharmaceutically acceptable salts thereof.

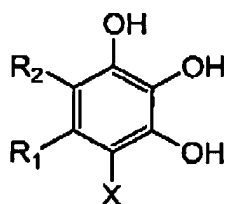
2. (Previously presented) The method of Claim 1 where only one active ingredient compound is administered.
3. (Previously presented) The method of Claim 1 where the mammal is a human.
4. (Currently amended) The method of Claim 3 where the amyloidosis is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and familial Mediterranean fever, the amyloidosis of multiple myeloma and B-cell dyscrasias, the amyloidosis of type II diabetes, the amyloidosis of the prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, the amyloidosis associated with long term hemodialysis, the amyloidosis associated with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with endocrine tumors.
5. (Currently amended) The method of Claim [[4]] 1, where the amyloidosis is Alzheimer's disease.
- 6-8. (Cancelled)
9. (Withdrawn) A method of treating a mammal suffering from a disease characterized by α -synuclein fibril formation, comprising administration to the mammal of a therapeutically effective amount of an isolated pure compound selected from the group consisting of the compounds of formula A, formula B, formula C, formula D, and formula E:

Applicant : Gerardo Castillo et al.
 Serial No. : 09/748,748
 Filed : December 26, 2000
 Page : 5 of 17

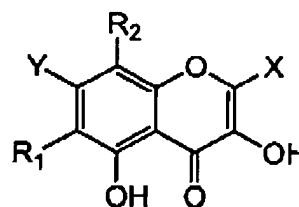
Attorney's Docket No.: 17170-002001



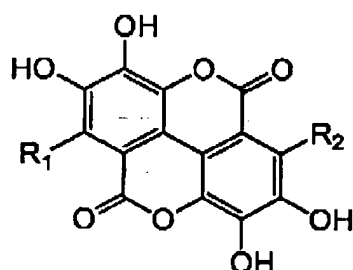
Formula A



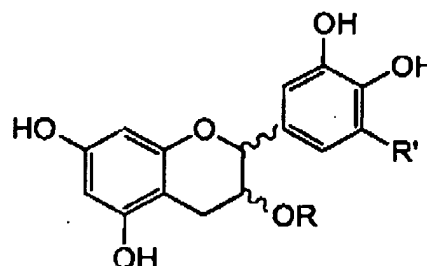
Formula B



Formula C



Formula D



Formula E

where:

R is selected from the group consisting of hydrogen, 2,3-dihydroxybenzoyl, 3,4-dihydroxybenzoyl, 2,3,4-trihydroxybenzoyl, and 3,4,5-trihydroxybenzoyl;

R' is hydrogen or OH;

R₁ and R₂ are independently selected from hydrogen and non-interfering substituents;

X is selected from hydrogen and the group consisting of

- hydroxy, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, and cycloamino,
- C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₁₋₂₂ alkylthio, and C₁₋₂₂ alkylcarboxyl, each optionally substituted with 1 to 5 moieties selected from the group consisting of halogen, hydroxy, mercapto, amino, nitro, C₁₋₆ alkoxy, C₁₋₆ alkylthio, and C₁₋₆ alkylcarboxyl,
- aromatic and heteroaromatic groups substituted with 2 or 3 adjacent hydroxy groups, and optionally substituted with 1 to 5 non-interfering substituents,
- sugars, optionally substituted with one or more anionic groups selected from sulfate, phosphate, phosphonate, carboxylate, and sulfonate groups,
- peptides and peptide derivatives, and

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 6 of 17

Attorney's Docket No.: 17170-002001

(f) $-C(O)R_3$ and $-C(O)OR_3$ (where R_3 is selected from the group consisting of (a) through (e) above); and

Y is hydrogen, hydroxy, C_{1-6} alkoxy, benzyloxy (where the phenyl group is optionally substituted with 1 to 3 substituents selected from halo and C_{1-6} alkyl), or $-OSO_2R_4$ (where R_4 is C_{1-6} alkyl or phenyl optionally substituted with 1 to 3 substituents selected from halo and C_{1-6} alkyl);

and the group of compounds consisting of acacetin, actinorhodine, alizarin, alizarin blue, alizarin orange, alizarinsulfonic acid, alkannin, anthragallol, anthralin, anthrarobin, anthrurufin, apigenin, apigetrin, apiose, baicalein, baptigenin, 1,2,4-benzenetriol, bostrycoidin, carbidopa, carminic acid, carubicin, cellobiose, centaurein, chloranilic acid, chondrosine, chromotrope 2B, chromotropic acid, chrysamminic acid, chrysarobin, chrysin, chrysophanic acid, cichoriin, citrazinic acid, citromycetin, collinomycin, curvularin, cyanidin, cyanidin 3-glucoside, cyanidin 3-rhamnoglucoside, cyanidin 3,5-diglucoside, cyanidin 3-sophoroside, daphnetin, datiscetin, daunorubicin, delphinidin, deoxyepinephrine, diosmetin, diosmin, dioxethedrine, dopa, dopamine, doxorubicin, droxidopa, echinochrome A, embelin, emodin, ergoflavin, eriodictyol, esculetin, fenoldopam, fomecin A, fomecin B, fraxetin, fraxin, fredericamycin A, fumigatin, fusarubin, fuscine, fustin, galangin, gallein, gallocyanine, gardenin A, gardenin B, gardenin C, gardenin D, gardenin E, genistein, gentisin, granaticin, guamecycline, hematein, hydroxysophorobioside, hydroxysophoricoside, icariin, isoquercitrin, kaempferol, kermesic acid, laccaic acid A, laccaic acid B, laccaic acid C, laccaic acid D, leucocyanidin, luteolin, maclurin, menogaril, methylenedigallic acid, morin, oosporein, phenicin, phloroglucide, puberulic acid, puberulonic acid, purpurin, purpurogallin, quercetagenin, quercimritrin, quinalizarin, quinic acid, resistomycin, rhamnetin, rhein, rhodizonic acid, rhodomycin A, rhodomycin B, robinin, ruberythric acid, rufigallol, rutin, scutellarein, tannic acid, tetroquinone, tiron, troxerutin, and tunichrome B1,

but excluding pyrogallol,

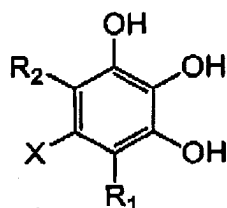
and the pharmaceutically acceptable salts thereof.

10. (Withdrawn) The method of Claim 9 where only one such compound is administered.

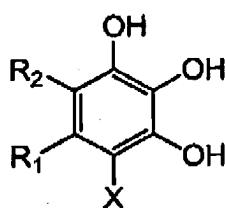
Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 7 of 17

Attorney's Docket No.: 17170-002001

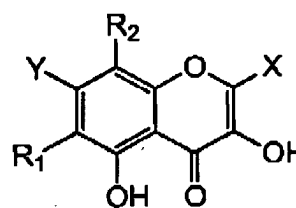
11. (Withdrawn) The method of Claim 10 where the mammal is a human.
12. (Withdrawn) The method of Claim 11 where the disease is Lewy body disease or Parkinson's disease.
13. (Withdrawn) The method of Claim 12 where the disease is Parkinson's disease.
14. (Withdrawn) A drug product for the treatment of a disease characterized by α -synuclein fibril formation in a mammal suffering therefrom, comprising a container labeled or accompanied by a label indicating that the drug product is for the treatment of a disease characterized by α -synuclein fibril formation, the container containing one or more dosage units each comprising at least one pharmaceutically acceptable excipient and, as an active ingredient, an isolated pure compound selected from the group consisting of the compounds of formula A, formula B, formula C, formula D, and formula E:



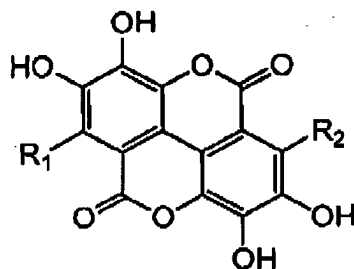
Formula A



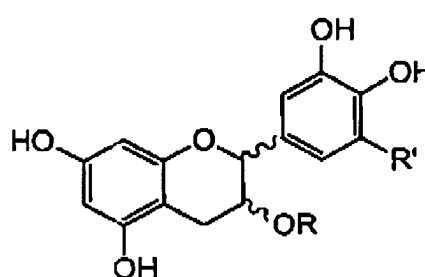
Formula B



Formula C



Formula D



Formula E

where:

R is selected from the group consisting of hydrogen, 2,3-dihydroxybenzoyl, 3,4-dihydroxybenzoyl, 2,3,4-trihydroxybenzoyl, and 3,4,5-trihydroxybenzoyl;

R' is hydrogen or OH ;

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 8 of 17

Attorney's Docket No.: 17170-002001

R_1 and R_2 are independently selected from hydrogen and non-interfering substituents;

X is selected from hydrogen and the group consisting of

- (a) hydroxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and cycloamino,
- (b) C_{1-22} alkyl, C_{1-22} alkoxy, C_{1-22} alkylthio, and C_{1-22} alkylcarboxyl, each optionally substituted with 1 to 5 moieties selected from the group consisting of halogen, hydroxy, mercapto, amino, nitro, C_{1-6} alkoxy, C_{1-6} alkylthio, and C_{1-6} alkylcarboxyl,
- (c) aromatic and heteroaromatic groups substituted with 2 or 3 adjacent hydroxy groups, and optionally substituted with 1 to 5 non-interfering substituents,
- (d) sugars, optionally substituted with one or more anionic groups selected from sulfate, phosphate, phosphonate, carboxylate, and sulfonate groups,
- (e) peptides and peptide derivatives, and
- (f) $-C(O)R_3$ and $-C(O)OR_3$ (where R_3 is selected from the group consisting of (a) through (e) above); and

Y is hydrogen, hydroxy, C_{1-6} alkoxy, benzyloxy (where the phenyl group is optionally substituted with 1 to 3 substituents selected from halo and C_{1-6} alkyl), or $-OSO_2R_4$ (where R_4 is C_{1-6} alkyl or phenyl optionally substituted with 1 to 3 substituents selected from halo and C_{1-6} alkyl);

and the group of compounds consisting of acacetin, actinorhodine, alizarin, alizarin blue, alizarin orange, alizarinsulfonic acid, alkannin, anthragallol, anthralin, anthrarobin, antharufin, apigenin, apigetrin, apiose, baicalein, baptigenin, 1,2,4-benzenetriol, bostrycoidin, carbidopa, carminic acid, carubicin, cellobiose, centaurein, chloranilic acid, chondrosine, chromotrope 2B, chromotropic acid, chrysamminic acid, chrysarobin, chrysin, chrysophanic acid, cichoriin, citrazinic acid, citromyctin, collinomycin, curvularin, cyanidin, cyanidin 3-glucoside, cyanidin 3-rhamnoglucoside, cyanidin 3,5-diglucoside, cyanidin 3-sophoroside, daphnetin, datiscetin, daumorubicin, delphinidin, deoxyepinephrine, diosmetin, diosmin, dioxethedrine, dopa, dopamine, doxorubicin, droxidopa, echinochrome A, embelin, emodin, ergoflavin, eriodictyol, esculetin, fenoldopam, fomecin A, fomecin B, fraxetin, fraxin, fredericamycin A, fumigatin, fusarubin, fuscin, fustin, galangin, gallein, gallocyanine, gardenin A, gardenin B, gardenin C,

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 9 of 17

Attorney's Docket No.: 17170-002001

gardenin D, gardenin E, genistein, gentisin, granaticin, guamecycline, hematein, hydroxysophorobioside, hydroxysophoricoside, icariin, isoquercitrin, kaempferol, kermesic acid, laccaic acid A, laccaic acid B, laccaic acid C, laccaic acid D, leucocyanidin, luteolin, maclurin, menogaril, methylenedigallic acid, morin, oosporein, phenicin, phloroglucide, puberulic acid, puberulonic acid, purpurin, purpurogallin, quercetagenin, quercimritrin, quinalizarin, quinic acid, resistomycin, rhamnetin, rhein, rhodizonic acid, rhodomycin A, rhodomycin B, robinin, ruberythric acid, rufigallol, rutin, scutellarein, tannic acid, tetroquinone, tiron, troxerutin, and tunichrome B1, but excluding pyrogallol, and the pharmaceutically acceptable salts thereof.

15. (Withdrawn) The drug product of Claim 14 containing only one such compound.

16. (Withdrawn) The drug product of Claim 15 indicated for the treatment of Parkinson's disease.

17. (Previously presented) The method of Claim 1 where R_1 and R_2 are independently selected from the group consisting of hydrogen; C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} alkylthio, in each of which the alkyl group is optionally substituted with 1 to 5 halogen atoms; and halo.

18. (Previously presented) The method of Claim 1 where X is selected from hydrogen and the group consisting of

(a) hydroxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and cycloamino,

(b) C_{1-22} alkyl, C_{1-22} alkoxy, C_{1-22} alkylthio, and C_{1-22} alkylcarboxyl, each optionally substituted with 1 to 5 moieties selected from the group consisting of halogen, hydroxy, mercapto, amino, nitro, C_{1-6} alkoxy, C_{1-6} alkylthio, and C_{1-6} alkylcarboxyl,

(c) aromatic and heteroaromatic groups substituted with 2 or 3 adjacent hydroxy groups, and optionally substituted with 1 to 5 non-interfering substituents, and

(d) $-C(O)R_3$ and $-C(O)OR_3$, where R_3 is selected from the group consisting of (a) through (c) above.

19. (Previously presented) The method of Claim 1 where X is selected from hydrogen and the group consisting of hydroxy, amino, $-C(O)R_3$, and $-C(O)OR_3$, where R_3 is selected from

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 10 of 17

Attorney's Docket No.: 17170-002001

hydroxy, amino, C₁₋₆ alkyl optionally substituted with 1 to 5 halogen atoms, and aromatic and heteroaromatic groups substituted with 2 or 3 adjacent hydroxy groups and optionally substituted with 1 to 5 non-interfering substituents selected from halogen atoms and C₁₋₆ alkyl and C₁₋₆ alkoxy, each optionally substituted with 1 to 5 halogen atoms.

20. (Previously presented) The method of Claim 1 where Y is selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkoxy, and benzyloxy, where the phenyl group is optionally substituted with 1 to 3 substituents selected from halo and C₁₋₆ alkyl and C₁₋₆ alkoxy, each optionally substituted with 1 to 5 halogen atoms.

21. (Previously presented) The method of Claim 1 where the compound is a compound of formula A or formula B, or a pharmaceutically acceptable salt thereof.

22. (Previously presented) The method of Claim 21 where the compound is selected from the group consisting of dibromogallic acid, digallic acid, ethyl gallate, exifone, fisetin, gallacetophenone, gallamide, gallic acid, α -glucogallin, β -glucogallin, 5-hydroxydopamine, and propyl gallate, and the pharmaceutically acceptable salts thereof.

23. (Previously presented) The method of Claim 1 where the compound is a compound of formula C or a pharmaceutically acceptable salt thereof.

24. (Previously presented) The method of Claim 23 where the compound is selected from the group consisting of myricetin and quercetin, and the pharmaceutically acceptable salts thereof.

25. (Previously presented) The method of Claim 1 where the compound is a compound of formula D or a pharmaceutically acceptable salt thereof.

26. (Previously presented) The method of Claim 25 where the compound is ellagic acid or a pharmaceutically acceptable salt thereof.

27. (Previously presented) The method of Claim 1 where the compound is a compound of formula E or a pharmaceutically acceptable salt thereof.

28. (Previously presented) The method of Claim 27 where the compound is selected from the group consisting of catechin, epicatechin, galocatechin, epigallocatechin, and their gallate esters, and the pharmaceutically acceptable salts thereof.

Applicant : Gerardo Castillo et al.
Serial No. : 09/748,748
Filed : December 26, 2000
Page : 11 of 17

Attorney's Docket No.: 17170-002001

29. (Previously presented) The method of Claim 1 where the active ingredient is selected from group of compounds consisting of acacetin, actinorhodine, alizarin, alizarin blue, alizarin orange, alizarinsulfonic acid, alkannin, anthragallol, anthralin, anthrarobin, antharufin, apigenin, apigetrin, apiose, baicalein, baptigenin, 1,2,4-benzenetriol, bostrycoidin, carbidopa, carminic acid, carubicin, cellobiose, centaurein, chloranilic acid, chondrosine, chromotrope 2B, chromotropic acid, chrysamminic acid, chrysarobin, chrysin, chrysophanic acid, cichoriin, citrazinic acid, citromycetin, collinomycin, curvularin, cyanidin, cyanidin 3-glucoside, cyanidin 3-rhamnoglucoside, cyanidin 3,5-diglucoside, cyanidin 3-sophoroside, daphnetin, datiscetin, daunorubicin, delphinidin, deoxyepinephrine, diosmetin, diosmin, dioxethedrine, dopa, dopamine, doxorubicin, droxidopa, echinochrome A, embelin, emodin, ergoflavin, eriodictyol, esculetin, fenoldopam, fomecin A, fomecin B, fraxetin, fraxin, fredericamycin A, fumigatin, fusarubin, fuscine, fustin, galangin, gallein, gallocyanine, gardenin A, gardenin B, gardenin C, gardenin D, gardenin E, genistein, gentisin, granaticin, guamecyclyne, hematein, hydroxysophorobioside, hydroxysophoricoside, icariin, isoquercitrin, kaempferol, kermesic acid, laccaic acid A, laccaic acid B, laccaic acid C, laccaic acid D, leucocyanidin, luteolin, maclurin, menogaril, methylenedigallic acid, morin, oosporein, phenicin, phloroglucide, puberulic acid, puberulonic acid, purpurin, purpurogallin, pyrocatechol, quercetagenin, quercimritrin, quinalizarin, quinic acid, resistomycin, rhamnetin, rhein, rhodizonic acid, rhodomycin A, rhodomycin B, robinin, ruberythric acid, rufigallol, rutin, scutellarein, tannic acid, tetroquinone, tiron, troxerutin, and tunichrome B1, and the pharmaceutically acceptable salts thereof.

30. (Previously presented) The method of Claim 1 where the compound is selected from 1,2,4-benzenetriol, ellagic acid, ethyl gallate, exifone, gallamide, gallic acid, 5-hydroxydopamine, myricetin, phloroglucide, propyl gallate, quercetin, quinic acid, and tannic acid, and the pharmaceutically acceptable salts thereof.